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Supplementary appendix

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Sorafenib in locally advanced or metastatic, radioactive iodine-refractory, differentiated thyroid cancer: a randomized, double-blind, phase 3 trial

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Supplementary Appendices

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Appendix B. Randomization and dose modifications

Randomization lists (one list for each of the six strata) were prepared by a separate Bayer randomization management (RM) group handling randomization tasks. All versions of the randomization list were stored electronically. The printout or the lists on the electronic storage media were stored by RM in a secure location with access only by the RM group, the external randomization process service provider, and the external provider responsible for providing data monitoring committee reviews. After primary completion of the study, the treatment information was released to Bayer data management for unblinding the study database.

Table B1. Dose reduction levels for sorafenib and placebo

	Dose level 0	Dose level -1	Dose level -2	Dose level -3
Sorafenib total daily dose, mg	800	600	400	200
Administration	2 x 200 mg tablets twice a day	2 x 200 mg and 1 x 200 mg tablet 12 hours apart (either could be given first)	1 x 200 mg tablet twice a day	1 x 200 mg tablet once a day
Placebo administration	2 tablets twice a day	2 tablets and 1 tablet 12 hours apart (either could be given first)	1 tablet twice a day	1 tablet once a day

Table B2. Criteria for dose delay or dose modification of sorafenib or placebo due to haematologic

adverse events

Grade of haematologic adverse event	Dose delay	Dose modification
Grade 0–2	No delay	No change
Grade 3	No delay	DECREASED one dose level[b]
Grade 4	DELAYED until ≤grade 2[a]	DECREASED two dose levels[b]

[a]If no recovery after 30-day delay, treatment was discontinued unless the patient was deriving clinical benefit.
[b]If another dose reduction after dose level -3 was required, treatment was discontinued.

Table B3. Criteria for dose delay or dose modification of sorafenib or placebo due to nonhaematologic

adverse events (except skin toxicity and hypertension)[a]

Grade of nonhaematologic adverse event[a]	Dose delay	Dose modification
Grade 0–1	No delay	No change
Grade 2	No delay	DECREASED one dose level[c,d]
Grade 3: 1st occurrence	DELAYED[b] until ≤grade 2	DECREASED one dose level[c,d]
Grade 3: no improvement within 7 days, or 2nd or 3rd occurrence	DELAYED[b] until ≤grade 2	DECREASED two dose levels[c,d]
Grade 3: 4th occurrence		DECREASED three dose levels[c,d]
Grade 4	Discontinued from protocol therapy	Discontinued from protocol therapy

[a]Also excluded nausea/vomiting that had not been premedicated, and diarrhoea.
[b]If no recovery after 30-day delay, treatment was discontinued unless patient was deriving clinical benefit.
[c]If another dose reduction after dose level -3 was required, treatment was discontinued.
[d]For patients who required a dose reduction for grade 2 or grade 3 toxicities, the dose of study drug may have been increased to the starting dose or up one dose level after one full cycle of therapy had been administered with the reduced dose without the appearance of the toxicity >grade 1.

Table B4. Criteria for dose modification of sorafenib or placebo due to hypertension

CTCAE grade of hypertension	Management/next dose
Grade 1	Increased BP monitoring considered
Grade 2 asymptomatic and diastolic BP <110 mm Hg	Begin antihypertensive therapy and continue study drug
Grade 2 symptomatic/persistent *or* diastolic BP ≥110 mm Hg *or* Grade 3	1. Study drug delayed[a] until symptoms resolved and diastolic BP ≤100 mm Hg, and patient treated with antihypertensives. When the study drug was restarted, it was reduced by one dose level[b] 2. If diastolic BP not controlled (≤100 mm Hg) on therapy, study drug was reduced another dose level[c]
Grade 4	Discontinued from protocol therapy

BP, blood pressure; CTCAE, Common Terminology Criteria for Adverse Events

[a]Patients requiring a delay of >14 days had to discontinue study drug.

[b]Patients may have been able to resume full dose later once BP was adequately controlled.

[c]Patients requiring >2 dose reductions had to discontinue study drug.

Table B5. Criteria for dose modification of sorafenib or placebo due to skin toxicity

Grade of skin toxicity[a]		Suggested dose modification
Grade 1	Any occurrence	Maintained dose level and instituted supportive measures immediately for symptomatic relief
Grade 2[b]	1st occurrence	Instituted supportive measures immediately and considered a decrease of sorafenib dose by one dose level. If no improvement within 7 days, see below
	No improvement within 7 days or 2nd occurrence	Interrupted until resolved to grade 0–1 When treatment resumed, decreased dose by one dose level
	3rd occurrence	Interrupted until resolved to grade 0–1 When treatment resumed, decreased dose by two dose levels
	4th occurrence	Discontinued from protocol therapy
Grade 3[b]	1st occurrence	Interrupted until resolved to grade 0–1 When treatment resumed, decreased dose by one dose level
	2nd occurrence	Interrupted until resolved to grade 0–1 When treatment resumed, decreased dose by two dose levels
	3rd occurrence	Discontinued from protocol therapy

[a]Dermatologic events were graded according to the Common Terminology Criteria for Adverse Events with the exception of hand–foot skin reactions, which were graded as follows:

grade 1 (numbness, dysesthesia/paresthesia, tingling, painless swelling or erythema of the hands and/or feet and/or discomfort that did not disrupt normal activities);

grade 2 (painful erythema and swelling of the hands and/or feet and/or discomfort that affected the patient's activities);

grade 3 (moist desquamation, ulceration, blistering or severe pain of the hands and/or feet and/or severe discomfort that caused the patient to be unable to work or perform activities of daily living).

[b]For patients who required a dose reduction for grade 2 or 3 rash or HFSR, the dose of study drug may have been increased to the starting dose after one full cycle of reduced dose therapy had been administered and there had been no appearance of rash or HFSR ≥grade 1.

Appendix C: Primary and key secondary endpoints

The primary endpoint was progression-free survival, assessed every 8 weeks by central independent blinded review using Response Evaluation Criteria in Solid Tumors (RECIST) v1.0, from the date of randomization to the date of radiological progression or death. Radiological progression in bone as defined in RECIST v1.0 was modified specifically in this protocol as follows: 1) radiological appearance of new lesions; 2) $\geqslant$20% increase in the sum of the longest diameter of all target lesions, which may include bone lesions if they have measurable soft tissue components; 3) bone lesions that require external radiation. Secondary endpoints included overall survival (measured from the date of randomization to the date of death), time to progression (TTP; measured from the date of randomization to the date of radiological progression), objective response rate (complete or partial response), disease control rate (complete or partial response, or stable disease), and duration of response (defined as the time from the first documented objective response until disease progression or death). FDG-PET scan at baseline was required in centres with access to PET scanners. PFS, OS and TTP were analyzed in all randomized patients. ORR and DCR were analyzed in patients who received study medication and had a baseline and a post-baseline tumor evaluation.
Tumour response and progression-free survival were evaluated by both central review and investigator assessment. Primary and secondary efficacy endpoints were based on central review during the double-blind period; unblinding and starting open-label sorafenib was decided by investigator assessment.

1 **Appendix D. Additional biomarker data**

2 **Table D1. Mutations tested in the HRAS, KRAS, NRAS, and BRAF genes**

Oncogene	Mutations assayed
HRAS	G12V/D, G13C/R/S, Q61H/H, Q61L/R/P, Q61K
KRAS	G12C, G12R, G12S, G12V, G12A, G12F, G13V/D, A59T, Q61E/K, Q61L/R/P, Q61H/H
NRAS	G12V/A/D, G12C/R/S, G13V/A/D, G13C/R/S, A18T, Q61L/R/P, Q61H, Q61E/K
BRAF	G464R, G464V/E, G466R, F468C, G469S, G469E, G469A, G469V, G469R, D594V/G, F595L, G596R, L597S, L597R, L597Q, T599I, V600E, V600K, V600L, K601N, K601E

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4   **Table D2. Demographic and clinical characteristics of the subpopulation for genetic analysis, compared with the overall study**

5   **population**

	Overall population (N=417)	Subpopulation for genetic analysis		
		Overall (n=256)	Sorafenib (n=126)	Placebo (n=130)
Sorafenib PFS benefit				
Hazard ratio	0·59	0·57		
95% confidence interval	0·45–0·76	0·42–0·78	NA	NA
P value	<0·001	<0·001		
Female, n (%)	218 (52·3)	129 (50·4)	59 (46·8)	70 (53·8)
Age, median (range)	63 (24–87)	63 (24–87)	63 (24–81)	64 (30–87)
Ethnicity, n (%)				
White	251 (60·2)	180 (70·3)	86 (68·3)	94 (72·3)
Asian	99 (23·7)	29 (11·3)	14 (11·1)	15 (11·5)
Black	11 (2·6)	9 (3·5)	5 (4·0)	4 (3·1)
Other or not reported	56 (13·4)	38 (14·8)	21 (16·7)	17 (13·1)
ECOG performance status, n (%)				
0	259 (62·1)	162 (63·3)	80 (63·5)	82 (63·1)
1	143 (34·3)	85 (33·2)	41 (32·5)	44 (33·8)
2	13 (3·1)	7 (2·7)	4 (3·2)	3 (2·3)
Histology by central review, n (%)				
Papillary	237 (56·8)	156 (60·9)	74 (58·7)	82 (63·1)
Follicular	106 (25·4)	64 (25·0)	31 (24·6)	33 (25·4)
Poorly differentiated	40 (9·6)	32 (12·5)	18 (14·3)	14 (10·8)
Well differentiated	3 (0·7)	1 (0·4)	1 (0·8)	0
Nonthyroid	1 (0·2)	0	0	0
Medullary	1 (0·2)	0	0	0
Oncocytic carcinoma	2 (0·5)	1 (0·4)	1 (0·8)	0
Carcinoma, not otherwise specified	3 (0·7)	0	0	0
Missing/nondiagnostic	27 (6·5)	2 (0·8)	1 (0·8)	1 (0·8)

6   ECOG, Eastern Cooperative Oncology Group; NA, not applicable

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7 **Table D3. Prognostic significance of BRAF and RAS mutation status on progression-free survival: multivariate model in**

8 **patients treated with sorafenib and placebo including BRAF, RAS, clinical variables, and histology as covariates**

| Variable	Level	Progression-free survival					
		Full analysis			Papillary patients only		
		HR	95% CI	P-value*	HR	95% CI	P-value*
N (events)			254 (154)			155 (89)	
Treatment	Sorafenib/placebo	0·50	0·36–0·69	<0·001	0·46	0·30–0·72	<0·001
Sex	Male/female	1·10	0·80–1·52	0·559	1·05	0·68–1·61	0·825
Ethnic origin	Other/white	0·76	0·48–1·21	0·246	0·77	0·43–1·38	0·379
	Not reported/white	0·86	0·54–1·38	0·539	0·85	0·45–1·61	0·620
Age		0·99	0·97–1·00	0·048	0·98	0·96–1·00	0·068
Histology	Follicular/papillary	1·37	0·90–2·07	0·138			
	Poorly differentiated/papillary	1·69	1·03–2·77	0·039			
	Other/papillary	1·02	0·31–3·39	0·972			
ECOG PS	1+2/0	1·36	0·97–1·92	0·075	0·92	0·58–1·45	0·714
BRAF	Mutation/wild-type	0·70	0·45–1·09	0·119	0·67	0·41–1·10	0·115
RAS	Mutation/wild-type	1·38	0·90–2·11	0·135	1·69	0·93–3·05	0·083

9 CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio

10 * P-values uncorrected for multiple hypothesis testing.

11 **Figure D1: Predictive analysis of biomarkers**

12 Kaplan–Meier graphs of progression-free survival by biomarker subgroups: BRAF mutation (P-value for
13 biomarker-treatment interaction =0·653) [panels a and b]; RAS mutation (P-value for biomarker-treatment
14 interaction =0·422) [panels c and d]; and thyroglobulin P-value for biomarker-treatment interaction =0·909)
15 [panels e and f]. Similar results were seen when thyroglobulin was analysed as a continuous variable (P-value
16 for biomarker-treatment interaction =0·988). Baseline median thyroglobulin =449·4 ng/ml.
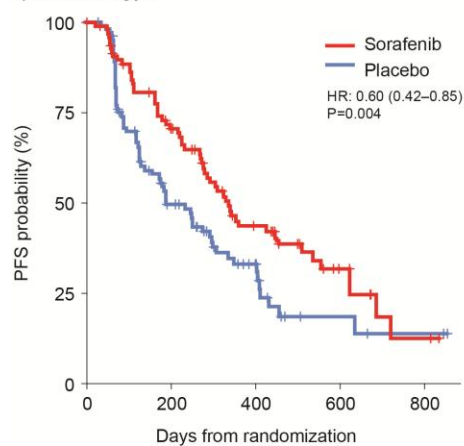
a) BRAF wild-type
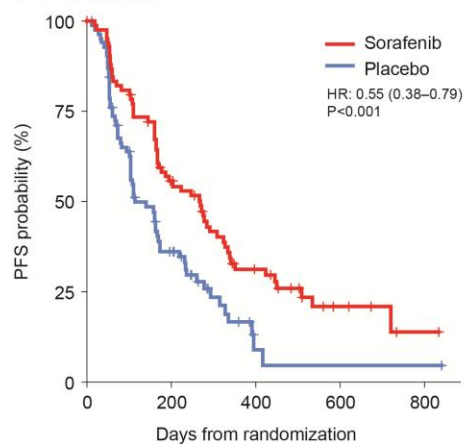
BRAF	Treatment	n	Events	Median PFS, days (months)	95% CI
WT	Sorafenib	92	59	271 (8.9)	170–337
WT	Placebo	87	64	117 (3.8)	106–175

b) BRAF mutation
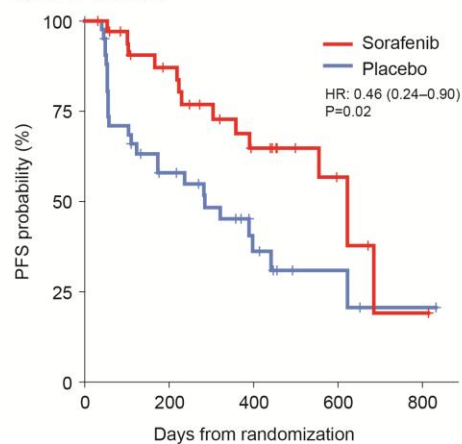
BRAF	Treatment	n	Events	Median PFS, days (months)	95% CI
MT	Sorafenib	34	14	623 (20.5)	393–NR
MT	Placebo	43	25	286 (9.4)	174–NR

c) RAS wild-type

RAS	Treatment	n	Events	Median PFS, days (months)	95% CI
WT	Sorafenib	102	60	329 (10.8)	272–451
WT	Placebo	104	69	175 (5.7)	113–284

d) RAS mutation
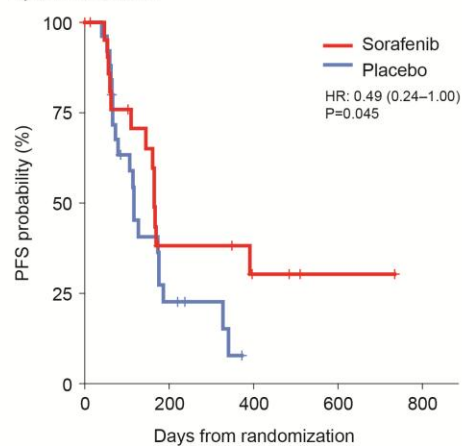
RAS	Treatment	n	Events	Median PFS, days (months)	95% CI
MT	Sorafenib	24	13	167 (5.5)	146–NR
MT	Placebo	26	20	105 (3.4)	69–175

e) Low baseline TG
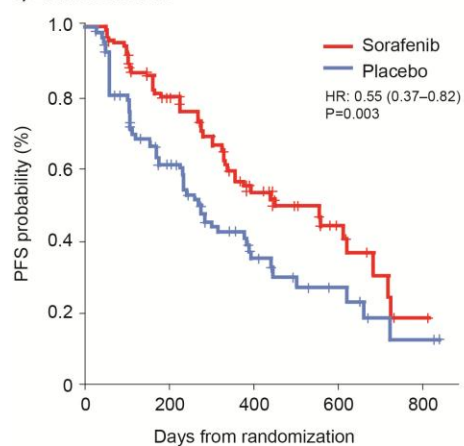
BL TG	Treatment	n	Events	Median PFS, days (months)	95% CI
Low	Sorafenib	98	60	556 (18.3)	354–722
Low	Placebo	103	60	268 (8.8)	223–391

f) High baseline TG
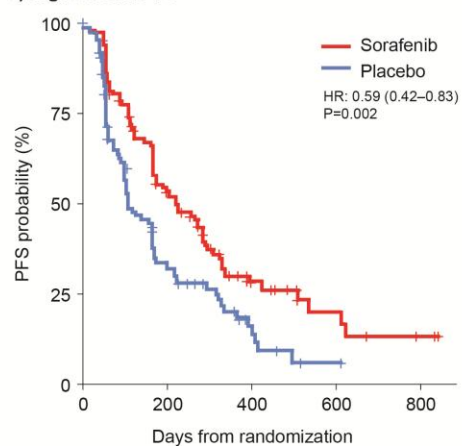
BL TG	Treatment	n	Events	Median PFS, days (months)	95% CI
High	Sorafenib	106	68	221 (7.3)	168–294
High	Placebo	96	70	113 (3.7)	105–169

CI, confidence interval; HR, hazard ratio; MT, mutation; NR, not reached; PFS, progression-free survival; TG, thyroglobulin; WT, wild-type

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